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*Published in:*  
British Journal of General Practice

*DOI:*  
[10.3399/bjgp17X690533](https://doi.org/10.3399/bjgp17X690533)

*Publication date:*  
2017

*Document Version*  
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

### *Citation for published version (APA):*

Baron Franco, B., McLean, G., Mair, F. S., Roger, V. L., Guthrie, B., & Mercer, S. W. (2017). Comorbidity and polypharmacy in chronic heart failure: a large cross-sectional study in primary care. *British Journal of General Practice*, 67(658), e314-e320. <https://doi.org/10.3399/bjgp17X690533>

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# **Comorbidity and polypharmacy in chronic heart failure: a cross-sectional study of 1.4 million patients in primary care**

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## How This Fits In

Comorbidity is known to be a common problem in patients with heart failure, but previous studies have been based on a small number of comorbid conditions using mainly non-primary care data sources. The current study compared prevalence rates of comorbidity in those with and without chronic heart failure due to left ventricular systolic dysfunction (LVSD) using nationally representative primary care data from 314 general practices and 1,421,756 patients in Scotland. Compared with standardised controls, the LVSD group had elevated comorbidity, with 25/31 physical and 6/7 mental health conditions being significantly more common. Polypharmacy of 11 or more drugs was also more common in the LVSD group.

# **Abstract**

## **Background**

Comorbidity is common in heart failure, but previous prevalence estimates have been based on a limited number of conditions using mainly non-primary care data sources.

## **Aim**

To compare prevalence rates of comorbidity and polypharmacy in those with and without chronic heart failure due to left ventricular systolic dysfunction (LVSD).

## **Design**

Cross-sectional study

## **Setting**

314 general practices and 1,421,756 patients in Scotland.

## **Methods**

Data on the presence of LVSD, 31 other physical and seven mental health comorbidities and prescriptions were extracted. Comorbidity prevalence were compared in patients with and without LVSD, standardised by age, gender and deprivation

## **Results**

17,285 people (1.2%) had a diagnosis of LVSD. Compared with standardised controls, the LVSD group had more comorbidity, with the biggest difference found for seven or more conditions (OR 4.10 95% CI 3.90-4.32). Twenty-five physical conditions and six mental health conditions were significantly more prevalent in those with LVSD relative to standardised controls. Polypharmacy was higher in the LVSD group compared with controls, with the biggest difference found for 11 or more repeat prescriptions (OR 4.81; 95% CI 4.60 to 5.04). However, these differences in polypharmacy were attenuated after controlling for

the number of morbidities, indicating that much of the additional prescribing was accounted for by multimorbidity rather than LVSD per se.

## **Conclusions**

Extreme comorbidity and polypharmacy is strikingly more common in patients with chronic heart failure due to LVSD. The efficient management of such complexity requires the integration of generalist and specialist expertise.

**Keywords:** heart failure; multimorbidity; general practice; comorbidity

## Introduction

Chronic heart failure constitutes a major public health problem.<sup>1, 2</sup> The prevalence of chronic heart failure is increasing,<sup>3,4</sup> and despite improvements in mortality,<sup>5</sup> approximately 50% of those diagnosed die within five years.<sup>6</sup> Chronic heart failure also impacts on quality of life<sup>7</sup> and increases “treatment burden”<sup>8, 9</sup> and challenging self-care demands.<sup>10</sup>

Patients with chronic disease often have multiple conditions<sup>11</sup>. More than half of all hospitalisations of heart failure patients are related to non-cardiovascular causes.<sup>12</sup> Comorbidity is common in heart failure,<sup>13,14,15</sup> especially in older patients.<sup>16,17</sup> Comorbidities in heart failure increase mortality and resource utilisation<sup>18,19, 20</sup> and worsen self care.<sup>21</sup>

However, much of this evidence on comorbidity in heart failure comes from studies of hospital discharge records, studies considering a relatively limited number of chronic conditions, or studies with relatively small sample sizes.<sup>22,23</sup> Data from primary care - the location of most health care interactions with heart failure patients - is scarce. The aim of the present study was to examine the prevalence of convergent and divergent comorbidity in chronic heart failure using a large, nationally representative cross-sectional UK primary care dataset. Polypharmacy was also examined.

## Methods

We used data from the Primary Care Clinical Informatics Unit at the University of Aberdeen on 1,424,378 individuals, aged 18 years or older, who were alive and permanently registered with 314 general practices (31% of all practices in Scotland) on March 31, 2007 registered with a participating practice. These practices had recorded routine electronic clinical data as part of the Scottish Programme for Improving Clinical Effectiveness in Primary Care (SPICE-PC), which was a voluntary scheme run by the Scottish Government, and was a nationally representative sample in terms of patients age, gender, and socioeconomic status.<sup>24</sup> Socioeconomic status was measured using the Carstairs score (grouped into quintiles). The dataset provided information on age, gender, socioeconomic status and 39 long term conditions. In total 18,899 individuals were identified as having heart failure through having a Read Code for heart failure recorded in their primary care electronic medical record (EMR). Heart failure due to left ventricular systolic dysfunction (LVSD) is one of a number of chronic conditions, whose accurate diagnosis and optimal management has been incentivised through the UK Quality and Outcomes Framework (QOF) pay-for-performance programme since 2004. We restricted analysis to 17,285 individuals who have been diagnosed heart failure due to LVSD who were identified using QOF indicator heart failure 03.<sup>25</sup> The control group were defined as the entire population of adults without LVSD.

To control for differences between the two populations in age, gender and deprivation levels we adopted a similar approach to that undertaken in previous papers<sup>26 27</sup> and generated standardised prevalence rates by age groups (18 to 24 years; 25 to 34; 35 to 44; 45 to 54; 55 to 64; 65 to 74; 75 to 84 and 85 and over), gender and deprivation quintile using the direct method. These age-gender-deprivation standardised rates were then used to calculate odds

ratio (ORs) and 95% confidence intervals (95% CI) for those with LVSD compared to those without (controls) for the prevalence of 31 physical conditions. There were seven mental health conditions (depression, alcohol misuse, learning disability, anorexia/bulimia, ‘anxiety and other neurotic, stress-related and somatoform disorders’, ‘schizophrenia and related conditions’, and dementia). For all statistical analyses, a p-value less than 0.05 was considered statistically significant. All analyses were performed in Stata version 13. The NHS Grampian Research Ethics Service approved the anonymous use of these data for research purpose.

## **Results**

### **Demographics**

There were 17,285 (1.2% of the sample) patients with a code for LVSD (table 1). Men were over-represented in the LVSD group compared to (unadjusted) controls (53.5% vs. 49.1% for controls;  $p < 0.001$ ). Individuals with LVSD were on average older (mean age 72.3 years vs. 47.6 years for controls;  $P < 0.001$ ). People with LVSD were marginally more likely to be living in the most deprived areas compared to unadjusted controls (LVSD most deprived quintile 20% vs controls 17.8%;  $p < 0.001$ ). Overall only 3.2% of individuals with heart failure had no other condition compared to 52.0% of unadjusted controls with no recorded condition (table 2)

### **Comorbidity: LVSD compared with standardised controls**



After standardising for age, sex and social deprivation (table 2) higher levels of comorbidity were evident in the LVSD group who were less likely to have none, one or two conditions but more likely to have three conditions (LVSD 17.5% vs. controls 4.0%; OR 4.10 95% CI 3.90-4.32). The biggest difference found was for seven or more conditions (LVSD 13.9% vs. controls 1.1%; OR 4.10 95% CI 3.90-4.32). A similar, though even more striking, pattern was found when restricting analysis to physical health comorbidities (table 2) with a five-fold difference between LVSD and controls being found in those with seven or more conditions (OR 5.10 (95% CI 4.79 to 5.43)).

Mental comorbidity was also more common in those with LVSD who were less likely to have no mental condition (LVSD 71.9% vs. controls 84.9%; OR 0.67 95% CI 0.65-0.70) and were more likely to have one, two or three or more mental health conditions ranging from OR 1.41 95% CI 1.36 to 1.47 (LVSD 20.3% vs. controls 11.5%) for one condition to OR 1.39 95% CI 1.19 to 1.61 (LVSD 20.3% vs. controls 11.5%) for three or more mental health conditions (table 2).

### **Physical health individual conditions: LVSD compared with controls**

For the LVSD group, 25 (including all 6 concordant conditions) out of 31 physical conditions were significantly more prevalent relative to controls (figure 1). The largest differences after standardisation for age, sex and deprivation were for ‘concordant’ conditions; coronary heart disease (CHD) (OR 7.98, 95% CI 7.72-8.25) atrial fibrillation (OR 6.84, 95% CI 6.57-7.12) and chronic kidney disease (CKD) (OR 3.81, 95% CI 3.18-3.46). However, large differences

were also found for non-cardiometabolic conditions such as chronic pain (OR 3.01, 95% CI 2.90-3.12) and COPD (OR 2.51, 95% CI 2.38-2.65).

### **Mental health conditions: LVSD compared with controls**

Table 3 highlights that those with LVSD had significantly higher prevalence for six of the mental health conditions with no difference found for anorexia/bulimia. The biggest difference after standardisation for age, sex and deprivation was for anxiety and stress related conditions (LVSD 11.0% vs. controls 3.8%; OR 1.83, 95% CI 1.73-1.94), followed by alcohol problems (LVSD 4.9% vs. controls 3.0%; OR 1.73, 95% CI 1.62-1.86). The highest prevalence for a mental health condition was found for depression with prevalence 16.3% for those with LVSD compared to 10.1% of controls (OR 1.48 95% CI 1.41-1.54.)

### **Polypharmacy: LVSD compared with controls**

Polypharmacy (defined as 5 or more repeat drugs) was substantially higher in the LVSD group compared with controls even after standardisation for age, gender, and deprivation (table 4). However, these differences were substantially attenuated after additional standardisation to account for the number of morbidities, indicating that much of the additional prescribing was accounted for by comorbidity rather than LVSD per se (see figure 2).

## **Discussion**

### **Summary**

This analysis has found that comorbidity of physical and mental health chronic conditions are more common in those with LVSD even after standardisation for age, sex and deprivation.

### **Strengths and limitations**

Strengths of our study were that we used a large nationally representative primary care database. We used LVSD as our measure for heart failure prevalence. The percentage of heart failure due to LVSD of 91.5% is similar to that found for all Scottish practices recorded in the QOF in the same year of 88.7%.<sup>28</sup> A limitation is that no data was available on the number of those with LVSD who had been identified using an echocardiogram. However, heart failure is routinely investigated in NHS Scotland using an echocardiogram. We included 39 morbidities in addition to LVSD, substantially more than most other studies of comorbidity and LVSD. However, the study was cross sectional and there was no data on outcomes.

### **Comparison with existing literature**

Direct comparison of the current study with existing literature is difficult as most previous studies have focused on the elderly, included a smaller number of conditions, not had a control group, and not been primary care based. However, the markedly higher prevalence of comorbidity in heart failure is consistent across studies, as is the finding of high levels of ‘concordant’ conditions such as CHD, CKD, and atrial fibrillation. The high level of chronic pain in the LVSD group in the present study appears to be a novel finding, which is worthy of further investigation.

It is possible of course that the higher level of comorbidities in LVSD in part reflects higher rates of diagnosis, since these patients would be invited for annual review under QOF. Similarly, the higher levels of polypharmacy could also relate to this and the fact that QOF recommends putting LVSD patients on at least two drugs (ACEi/ARB and b-blocker).

### **Implications for research and practice**

Recent heart failure clinical guidelines acknowledge the issue of comorbidity but do not address the specific challenges.<sup>29 30</sup> The evidence underpinning recommendations in LVSD guidelines is largely created from randomised controlled trials which exclude older and more comorbid individuals.<sup>31 32</sup> Many evidence gaps remain in the clinical management of comorbidity in LVSD. For example, the safety and efficacy of many treatments for comorbidities in the context of LVSD as well as the drugs recommended for LVSD remain uncertain.

In conclusion, the current study has provided a comprehensive picture of current patterns of comorbidity in primary care in those with chronic heart failure due to LVSD. Comorbidity is clearly the norm in LVSD. Clinical guidelines and health care services need to put greater emphasis on management of such complexity in LVSD, which will require the application and integration of generalist and specialist expertise.

## **Funding**

We thank the Chief Scientist Office of the Scottish Government Health Directorates (Applied Research Programme Grant ARPG/07/1); the Scottish School of Primary Care, which part-supported SWM's post and the development of the Applied Research Programme.

## **Ethics**

The NHS National Research Ethics Service had previously approved the anonymous use of these data for research purposes, therefore this study did not need individual ethics approval.

## **Competing Interests**

All authors declare that they have no competing interests

## **Acknowledgements**

We thank the Primary Care Clinical Informatics Unit at the University of Aberdeen, which provided the data, especially Katie Wilde and Fiona Chaloner of the University of Aberdeen, who did the initial data extraction and management.

**Table 1 Age, gender and deprivation status, LVSD versus controls**

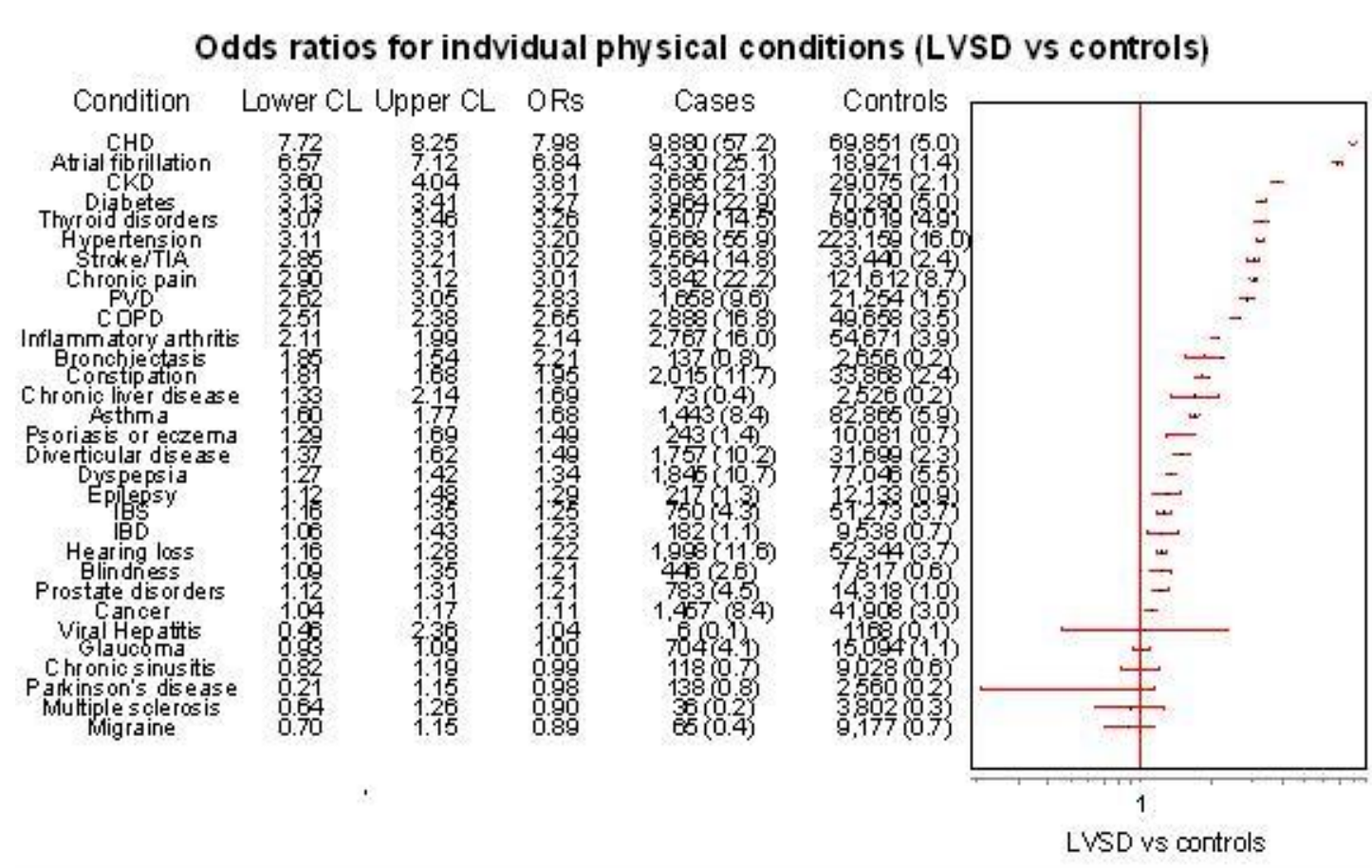
| <b>Variable</b>             | <b>LVSD<br/>N=17,825 (1.2% of all<br/>patients)<br/>No. (%)</b> | <b>Controls<br/>N=1,404,471 (98.8%) of all<br/>patients<br/>No. (%)</b> |
|-----------------------------|---|---|
| <b>Men</b>                  | 9,242 (53.5%)   | 88,967 (49.1%)  |
| <b>Mean Age (sd)</b>        | 72.3 (13.1)   | 47.6 (18.1)   |
| <b>Age Group</b>            |   |   |
| <b>18-24</b>                | 39 (0.2)  | 151,650 (10.8)  |
| <b>25-34</b>                | 126 (0.7)   | 229,266 (16.3)  |
| <b>35-44</b>                | 396 (2.3)   | 278,567 (19.8)  |
| <b>45-54</b>                | 1,129 (6.5)   | 252,579 (18.0)  |
| <b>55-64</b>                | 2,573 (14.9)  | 216,542 (15.4)  |
| <b>65-74</b>                | 4,654 (26.9)  | 150,120 (10.7)  |
| <b>75-84</b>                | 5,902 (31.2)  | 93,009 (6.6)  |
| <b>85 and over</b>          | 2,966 (17.3)  | 32,738 (2.3)  |
| <b>Deprivation quintile</b> |   |   |
| <b>Least Deprived</b>       | 3,526 (20.4)  | 268,122 (19.1)  |
| <b>2</b>                    | 3,531 (20.4)  | 300,086 (21.4)  |
| <b>3</b>                    | 3,644 (21.1)  | 317,963 (22.6)  |
| <b>4</b>                    | 3,127 (18.1)  | 267,710 (19.1)  |
| <b>Most deprived</b>        | 3,457 (20.0)  | 250,590 (17.8)  |

**Table 2 LVSD status and number of morbidities**

|                                       | <b>LVSD N (%)</b><br>N=17,285 | <b>Controls (%)</b><br>N=1,404,471 | <b>Age, gender and deprivation<br/>standardised Odds Ratio (95% CI)</b><br><sup>a</sup> |
|---------------------------------------|-------------------------------|------------------------------------|---|
| <b>Total number of morbidities</b>    |                               |                                    |   |
| None                                  | 558 (3.2)                     | 729,975(52.0)                      | 0.90 (0.10 to 0.80)   |
| One                                   | 1,831 (10.6)                  | 300,219 (21.4)                     | 0.47 (0.45 to 0.50)   |
| Two                                   | 2,555 (14.8)                  | 160,823 (11.5)                     | 0.77 (0.73 to 0.81)   |
| Three                                 | 3,023 (17.5)                  | 94,847 (6.8)                       | 1.22 (1.77 to 1.88)   |
| Four                                  | 2,835 (16.4)                  | 55,726 (4.0)                       | 1.67 (1.60 to 1.75)   |
| Five                                  | 2,375 (13.7)                  | 31,401 (2.2)                       | 2.23 (2.12 to 2.34)   |
| Six                                   | 1,707 (9.9)                   | 16,748 (1.2)                       | 2.75 (2.59 to 2.91)   |
| Seven or more                         | 2,401 (13.9)                  | 14,732 (1.1)                       | 4.10 (3.90 to 4.32)   |
| <b>Number of physical morbidities</b> |                               |                                    |   |
| None                                  | 635 (3.7)                     | 800,019 (57.0)                     | 0.90 (0.10 to 0.80)   |
| One                                   | 2,154 (12.5)                  | 292,513 (20.8)                     | 0.51 (0.49 to 0.54)   |
| Two                                   | 2,916 (16.9)                  | 147,369 (10.5)                     | 0.84 (0.81 to 0.88)   |
| Three                                 | 3,302 (19.1)                  | 81,222 (5.8)                       | 1.38 (1.32 to 1.44)   |
| Four                                  | 2,947 (17.1)                  | 43,876 (3.1)                       | 1.97 (1.89 to 2.06)   |
| Five                                  | 2,272 (13.1)                  | 22,241 (1.6)                       | 2.67 (2.54 to 2.81)   |
| Six                                   | 1,479 (8.6)                   | 10,261 (0.7)                       | 3.40 (3.20 to 3.62)   |
| Seven or more                         | 1,580 (9.1)                   | 6,970 (0.5)                        | 5.10 (4.79 to 5.43)   |
| <b>Number of mental morbidities</b>   |                               |                                    |   |
| None                                  | 12,425 (71.9)                 | 1,193,418 (84.9)                   | 0.67 (0.65 to 0.70)   |
| One                                   | 3,487 (20.3)                  | 161,011 (11.5)                     | 1.41 (1.36 to 1.47)   |
| Two                                   | 1,172 (6.8)                   | 42,968 (3.1)                       | 1.35 (1.27 to 1.43)   |
| Three or more                         | 201 (1.2)                     | 7,074 (0.5)                        | 1.39 (1.19 to 1.61)   |

p=<0.001 unless stated

**Figure 1. Prevalence and odds ratios for individual physical conditions (standardised by age, gender and deprivation score)**



Key; CHD=Coronary Heart Disease; CKD=Chronic Kidney Disease; PVD= Peripheral arterial disease; IBS=Irritable bowel syndrome; IBD=Inflammatory bowel disease .



**Table 3 Prevalence and odds ratios for individual mental conditions (standardised by age, gender and deprivation score)**

|   | <b>LVSD N (%)</b><br>N=17,285 | <b>Controls N (%)</b><br>N=1,404,471 | <b>Age, gender and deprivation<br/>standardised Odds Ratio<br/>(95% CI)</b> |
|---|-------------------------------|--------------------------------------|---|
| <b>Anxiety &amp; stress related</b>       | 1,906 (11.0)                  | 53,41 (3.8)                          | 1.83 (1.73 to 1.94)   |
| <b>Alcohol problems</b>                   | 851 (4.9)                     | 41,374 (3.0)                         | 1.73 (1.62 to 1.86)   |
| <b>Depression</b>                         | 2,810 (16.3)                  | 140,587 (10.1)                       | 1.52 (1.43 to 1.56)   |
| <b>Learning Disability</b>                | 57 (0.3)                      | 4,950 (0.4)                          | 1.50 (0.82 to 1.)   |
| <b>Dementia</b>                           | 562 (3.3)                     | 10,936 (0.8)                         | 1.45 (1.26 to 1.67)   |
| <b>Schizophrenia and bipolar disorder</b> | 199 (1.2)                     | 12,237 (0.9)                         | 1.19 (1.03 to 1.38) p=0.01  |
| <b>Anorexia or bulimia</b>                | 58 (0.3)                      | 5,235 (0.4)                          | 1.04 (0.87 to 1.39) p=0.34  |

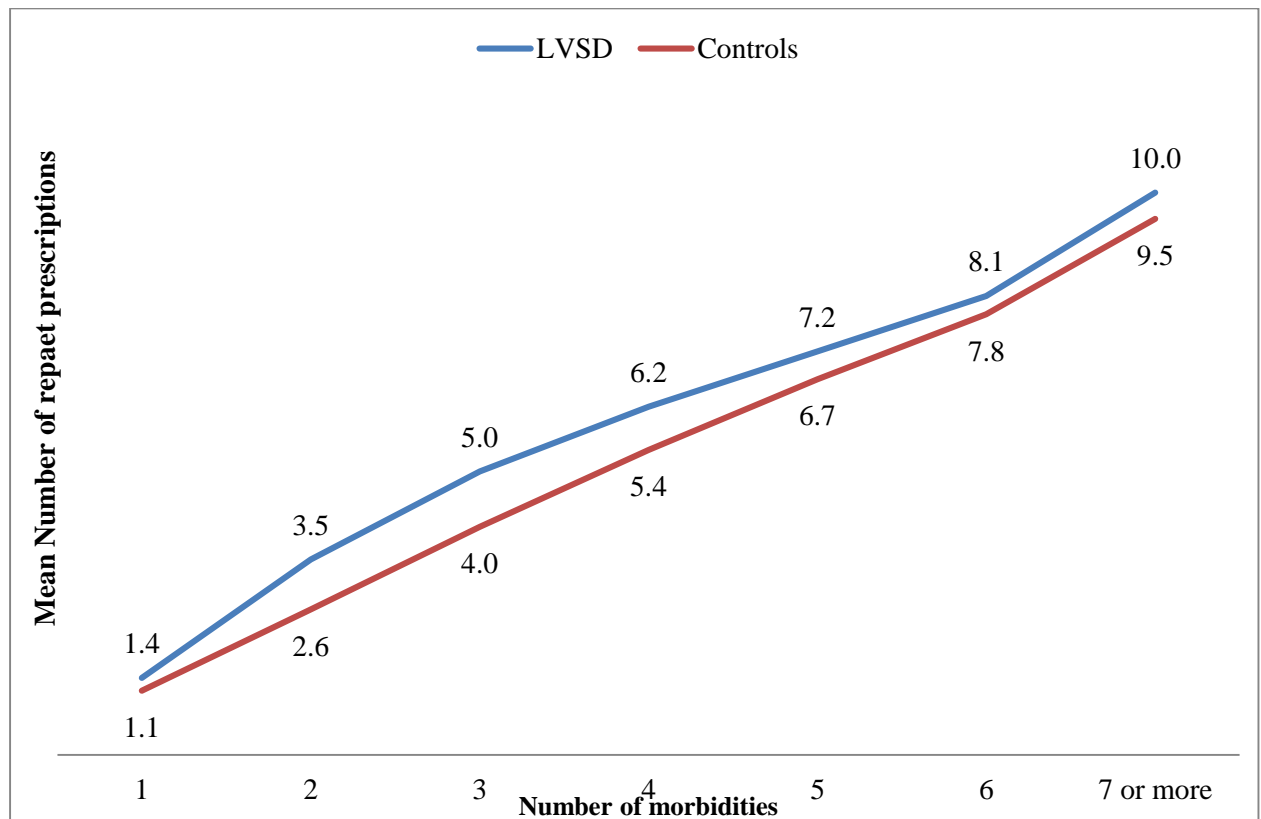
p=<0.001 unless stated

**Table 4 LVSD status and number of repeat medications**

| <b>Number of medications</b> | <b>LVSD N (%)</b><br>N=17,285 | <b>Controls N (%)</b><br>N=1,404,471 | <b>Age, gender and deprivation<br/>standardised Odds Ratio<br/>(95% CI)</b> | <b>Age, gender, deprivation and<br/>morbidity count<br/>standardised Odds Ratio<br/>(95% CI)</b> |
|------------------------------|-------------------------------|--------------------------------------|---|--|
| <b>None</b>                  | 1,322 (7.7%)                  | 864,813 (61.5%)                      | 0.16 (0.15 to 0.18)   | 0.46 (0.46 to 0.52)  |
| <b>One or two</b>            | 1,226 (7.1%)                  | 242,533 (17.2%)                      | 0.33 (0.31 to 0.35)   | 0.63 (0.59 to 0.67)  |
| <b>Three or four</b>         | 2,251 (13.0%)                 | 126,833 (9.0%)                       | 0.64 (0.61 to 0.67)   | 0.76 (0.72 to 0.79)  |
| <b>Five or six</b>           | 3,527 (20.4%)                 | 80,170 (5.7%)                        | 1.45 (1.39 to 1.51)   | 1.26 (1.21 to 1.32)  |
| <b>Seven or eight</b>        | 3,470 (20.1%)                 | 46,595 (3.3%)                        | 2.39 (2.29 to 2.49)   | 1.56 (1.49 to 1.63)  |
| <b>Nine or ten</b>           | 2,433 (14.1%)                 | 24,322 (1.7%)                        | 3.00 (2.85 to 3.14)   | 1.56 (1.48 to 1.64)  |
| <b>Eleven or more</b>        | 3,056 (17.7%)                 | 21,827 (1.6%)                        | 4.81 (4.60 to 5.04)   | 1.81 (1.72 to 1.91)  |

p=<0.001 unless stated

**Figure 2 Mean number of repeat prescriptions by number of morbidities in patients with LVSD and controls**



## References

<sup>1</sup>AHA Statistical Update. Heart Disease and Stroke Statistics – 2013 Update. A Report from the American Heart Association. *Circulation* 2013; 127: e6-e245.

<sup>2</sup> Mant J, Al-Mohammad A, Mark D. Royal College of Physicians. Chronic heart failure. National Clinical Guideline for Diagnosis and Management. *NICE Guideline*. 2010:1-646

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<sup>3</sup> Owan TE, Hodge DO, Herges RM et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;355:251-9.

<sup>4</sup> Stewart S, MacIntyre K, Capewell S et al. Heart failure and the aging population: an increasing burden in the 21st century? *Heart (British Cardiac Society)* 2003;89:49-53.

<sup>5</sup> Jhund PS, Macintyre K, Simpson CR et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation* 2009;119:515-23.

<sup>6</sup> Hobbs FD, Roalfe AK, Davis RC et al. Prognosis of all-cause heart failure and borderline left ventricular systolic dysfunction: 5 year mortality follow-up of the Echocardiographic Heart of England Screening Study (ECHOES). *Euro Heart J* 2007;28:1128-34.

<sup>7</sup> Hobbs FD, Kenkre JE, Roalfe AK et al. Impact of heart failure and left ventricular systolic dysfunction on quality of life: a cross-sectional study comparing common chronic cardiac and medical disorders and a representative adult population. *Euro Heart J* 2002;23:1867-76.

<sup>8</sup> Gallacher K, May C, Montori VM, et al. Understanding treatment burden in chronic heart failure. A qualitative study. *Ann Fam Med* 2011; 9:235-243

<sup>9</sup> Jani B, Blane D, Browne S et al. Identifying treatment burden as an important concept for end of life care in those with advanced heart failure. *Curr Opin Support Palliat Care*. 2013; 7:3-7

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<sup>10</sup> Browne S, Macdonald S, May CR et al. Patient, Carer and Professional Perspectives on Barriers and Facilitators to Quality Care in Advanced Heart failure. *Plos One* 2014 Mar 27;9(3):e93288

<sup>11</sup> Barnett K, Mercer SW, Norbury M et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380:37-43.

<sup>12</sup> Dunlay SM, Redfield MM, Weston SA et al. Hospitalisations after heart failure diagnosis: a community perspective. *J Am Coll Cardiol* 2009;54:1695-1702.

<sup>13</sup> Wong CY, Chaudrhy SI, Desai MM et al. Trends in Comorbidity, Disability, and Polypharmacy in Heart failure. *Am J Med* 2011; 124:136-143

<sup>14</sup> Ather SA, Chan W, Bozkurt B et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol* 2012;59 (11):998-1005

<sup>15</sup> Saczynski JS, Go AS, Magid DJ et al. Patterns of comorbidity in older adults with heart failure: the Cardiovascular Research Network PRESERVE study. *J Am Geriatr Soc.* 2013 Jan; 61(1):26-33. doi: 10.1111/jgs.

<sup>16</sup> Ahluwalia SC, Gross CP, Chaudhry SI et al. Change in comorbidity prevalence with advancing age among persons with heart failure. *J Gen Intern Med* 2011;26:1145-51

<sup>17</sup> Braunstein JB, Anderson GF, Gerstenblith G et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol* 2003;42:1226-33

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- <sup>18</sup> Ritchie C, Ekundayo OJ, Muchimba M et al. Effects of diabetes mellitus in patients with heart failure and chronic kidney disease: a propensity-matched study of multimorbidity in chronic heart failure. *Int J Cardiol.* 2009 May 29;134(3):330-5
- <sup>19</sup> Böhm M, Pogue J, Kindermann I et al. Effect of comorbidities on outcomes and angiotensin converting enzyme inhibitor effects in patients with predominantly left ventricular dysfunction and heart failure. *Eur J Heart Fail.* 2014 Mar; 16(3):325-33.
- <sup>20</sup> Blecker S, Herbert R, Brancati FL. Comorbid diabetes and end-of-life expenditures among Medicare beneficiaries with heart failure. *J Card Fail.* 2012 Jan; 18(1):41-6.
- <sup>21</sup> Dickson VV, Buck H, Riegel B. Multiple comorbid conditions challenge heart failure self-care by decreasing self-efficacy. *Nurs Res.* 2013 Jan-Feb;62(1):2-9
- <sup>22</sup> Murphy NF, Simpson CR, McAlister FA et al. National survey of the prevalence, incidence, primary care burden, and treatment of heart failure in Scotland. *Heart (British Cardiac Society)* 2004;90:1129-3
- <sup>23</sup> Hawkins NM, Jhund PS, McMurray JJV et al. Heart failure and socioeconomic status: accumulating evidence of inequality. *Eur J Heart Fail.* 2012;14:138-146.
- <sup>24</sup> Elder R, Kirkpatrick M, Ramsay W et al. Measuring quality in primary medical services using data from SPICE. Edinburgh, Scotland: *NHS National Services Scotland*, 2007.
- <sup>25</sup> NHS-Primary Care Commissioning. QOF implementation: business rules v 24.0, updated November 2012. <http://www-pcc.nhs.uk/145/>. (Accessed Feb 15, 2013)

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<sup>26</sup> Court H, McLean G, Guthrie B et al. Visual impairment and physical and mental health comorbidities in older adults: a cross-sectional study of 291,169 patients in primary care. *BMC Medicine* 2014, 12:181

<sup>27</sup> Smith DJ, Martin DJ, McLean G et al. Multimorbidity in bipolar disorder and under treatment of cardiovascular disease: cross sectional study. *BMC Medicine* 2013, 11:263-274

<sup>28</sup> <http://www.isdscotland.org/Health-Topics/General-Practice/Quality-And-Outcomes-Framework/>

<sup>29</sup> Yancy, C, Jessup, M, Bozkurt et al. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; 128: e240–e327.

<sup>30</sup> Guthrie B, Payne K, Alderson P et al. Adapting clinical guidelines to take account of multimorbidity. *BMJ* 2012, 345:e6341.

<sup>31</sup> Masoudi FA, Havranek EP, Wolfe P et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. *Am Heart J* 2003, 146(2):250-257.

<sup>32</sup> Van Spall HGC, Toren A, Kiss A et al. Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals: A Systematic Sampling Review. *JAMA* 2007, 297(11):1233-1240